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**Sustained-release preparations and the process thereof.**

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Sustained-release preparations essentially consisting of 1 part by weight of a water-soluble active ingredient and 1 to 10 parts by weight of two or more fats where the melting point is different in one from others, being capable of releasing active ingredients at a constant rate for a long-period of time, and being manufactured easily and economically.

**EP 0 351 580 A2**

## SUSTAINED-RELEASE PREPARATIONS AND THE PROCESS THEREOF

## BACKGROUND OF THE INVENTION

Field of Invention

This invention relates to long-acting preparations which have actions of both rapid-release and sustained-release in spite of their single unit dosage form, and also to the process of manufacturing said preparations. In the manufacturing process of this invention, neither organic solvents nor water are used. Therefore, there is no danger of explosion. Nor is there any problem of residual solvent. Besides it does not require drying process either. Thus, this process makes it possible to manufacture said sustained-release preparations easily and at a low cost.

Prior Art

Some methods have been reported concerning the technique of making sustained-release by effectively controlling the dissolution of water-soluble active ingredient with the use of melted fats. Such the technique is divided into two main types: one is a method of making sustained-release by forming a matrix or by making a solid dispersion and the other is that of making a membrane, reservoir type preparations by coating the fats.

The method disclosed in KOKOKU 63-24978 belongs to the latter and attains sustained-release extending over a period of 8 hours or longer by coating an emulsion of fats in water onto the active ingredient. However, this method has a drawback in that since a W/O type emulsion of fat is spray-coated on the granules prepared beforehand, (a) it involves processes of making granules and of drying the granules, (b) it also involves further processes of drying after spray coating, etc., and (c) it required the use of a surfactant in making an emulsion, by which a problem in safety is caused.

## SUMMARY OF INVENTION

The present invention provides sustained-release preparations essentially consisting of 1 part by weight of a water-soluble active ingredient and 1 to 10 parts by weight of two or more fats where the melting point is different in one from other and also provides unique processes for manufacturing said novel sustained-release preparations, characterized

in that 1 part by weight of a water-soluble active ingredient is suspended or melted in 1 to 10 parts by weight of a mixed melt consisting of two or more fats having different melting points, and while the temperature of the suspension or melt is maintained at a level higher than the solidification point of the fat having a higher melting point, said suspension or melt is formulated into granules by means of spray-cooling, and then the granules obtained are annealed at a temperature (hereinafter this temperature is mentioned as "annealing temperature") which is lower than the melting point of the fat having a higher melting point but is higher than the melting point of the fat having a lower melting point.

Thus prepared preparations attain zero-order release of drug for a long period of time.

## BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 shows the relationship between the amount of the active ingredient released from each preparation of this invention versus the lapse of time. The ordinate shows the dissolution rate (%) of PPA and abscissa shows the time. The curves indicated by ① - ⑤ are the dissolution curves on preparations of Examples 1 to 5 in the second fluid (Pharmacopoeia of Japan, 11th Edition), respectively.

Fig. 2 shows the relationship between the amount of the active ingredient released from the preparation of this invention versus the lapse of time. The ordinate shows the dissolution rate (%) of d-CPM and abscissa shows the time. The curve indicated by ① is the dissolution curve on the preparation of Example 6 in the first fluid and the curve ② is that in the second fluid.

Fig. 3 shows the relationship between the amount of the active ingredient released from each reference preparation versus the lapse of time. The ordinate shows the dissolution rate (%) of PPA and abscissa shows the time. The curves indicated by ① - ③ are the dissolution curves on preparations of Reference Examples 1 to 3 in the second fluid, respectively.

## DESCRIPTION OF PREFERRED EMBODIMENT

Problems to be solved

mentioned above, when sustained-release

preparations are made with the use of a melt of fats, it is impossible by a simple spray-coating method to obtain sophisticated zero-order controlled release of pharmaceutical substance. Therefore, special contrivances are used in coating, etc. as disclosed in KOKAI 63-24978. However, such processes are complicated, and take a long time to be done, which are the drawbacks of this method. In making conventional long-acting preparations, rapid-release preparations which are independently prepared have been admixed with sustained-release preparations, or a rapid releasing portion has been coated on sustained-release preparations, and so forth. However, such the operation are troublesome. Here is a weak point of the conventional method.

#### Means to solve the problems

In view of the above circumstances, the inventors tried to develop a simple method by which zero-order sustained-release preparations could be made (especially, without a drying process), and have perfected this invention, after strenuous studies. This invention relates to zero-order sustained-release preparations and to the process thereof. This invention provides simple and economic but unique methods of manufacturing zero-order sustained-release preparations capable of releasing active ingredient at a constant rate over a period of 10 hours or longer. In this manufacturing method, a melt or suspension of fats containing a water-soluble active ingredient is made into granules by a simple spray cooling and then the granules obtained are annealed.

A study of dissolution patterns on the sustained-release preparations manufactured by the method of this invention shows that there are two phases on drug releasing. One is located at an earlier stage where an active ingredient is first released rapidly, and the other is at the later stage where an active ingredient is released gradually. That is to say, 20 - 30% of the active ingredient is released rapidly within 10 minutes, and the rests are released at a zero-order over a long period of time. According to the method of this invention, preparations which give rapid and long-acting pharmacological effects can be readily manufactured at a low cost, without special process of making a rapid releasing part.

This invention is especially useful for the preparation of such active ingredients as being absorbed rapidly through an extensive area of the digestive tract but having short action. This invention does not exclude to coat, on the present sustained-release preparation, additional active ingredient as a rapid-release portion or the different

kind of active ingredients which should be released rapidly. By so doing, a wider range of preparations can be designed, thus making it possible to easily manufacture preparations with a desired pattern of release.

As for fats to be used in this invention, any fat can be used as long as it is pharmacologically inert and has no interaction with any of the water-soluble pharmaceutical active ingredients used. Representatives of such fats are exemplified below, showing their melting points in parentheses. It should be noted, however, that some of them are sold in various grades and melting points generally vary with the grade. Therefore, they should be used after confirming their melting points.

Hydrogenated castor oil (79-88°C), hydrogenated beef tallow (oil) (38-62°C), hydrogenated lard oil (38-62°C), cacao butter (45-50°C); fatty acid glycerol esters such as glycerol monolaurate (44-63°C), glycerol monomyristate (56-70.5°C), glycerol monopalmitate (66.5-77°C), glycerol mono-stearate (74.5°C), glycerol dilaurate (39-54°C), glycerol dimyristate (54-63°C), glycerol dipalmitate (50-72.5°C), glycerol distearate (71-77°C), glycerol trimyristate (44-55.5°C), glycerol tripalmitate (55.5-65.5°C), glycerol tristearate (64-73.1°C); wax material such as beeswax (60-67°C), carnauba wax (80-86°C), Japan wax (50-54°C), and spermaceti (42-54°C); hydrocarbons such as paraffin (50-75°C), microcrystalline wax (74-91°C); fatty alcohols such as cetyl alcohol (47-53°C), stearyl alcohol (56-62°C); and higher fatty acids such as lauric acid (42-42.2°C), myristic acid (53.4-53.6°C), palmitic acid (63.8-64.0°C), stearic acid (70.7°C), behenic acid (86-86.3°C), and arachic acid (77.5-77.7°C).

In the method of this invention, since two or more fats are used as a mixture, one having a higher melting point than the other is called fat having a higher melting point, and the other is called fat having a lower melting point. Therefore, in this invention, the term "higher melting point" or "lower melting point" does not mean the absolute values, but indicates a relative one in comparison between two or more fats selected. It is preferable that a fat having a melting point of 60°C or higher is used as one having higher melting point, and at the same time, it is preferable that there is a difference of at least 10°C between the melting points of the two fats to be used.

The sustained-release preparations of this invention are manufactured as follows: First, two fats having different melting points each other are selected, both of which are insoluble or sparingly soluble in water. Next, 1 part by weight of the fat having a higher melting point is mixed with 0.05 - 1.0 part by weight, preferably 0.2 - 0.5 part by weight, of the fat having a lower melting point, and

the mixture is heated at 90 - 120° C to give a melt. When the addition ratio of the fat having a lower melting point is higher than the upper limit mentioned above, it becomes difficult to maintain the original form of the granules through the manufacturing processes, and when the ratio is lower than the lower limit, it becomes impossible to obtain zero-order sustained-release preparations. Powdery active ingredient is added to the aforementioned melt at a rate of 10 - 100%, preferably 25- 100% by weight to the total weight of the fats employed, while the melt is kept at 100 - 120° C. Thus obtained suspension or melt is then subjected to spray cooling under the conditions at a spraying temperature of 110° C and at a cooling temperature of 20-40° C, whereby homogenized granules or beads are obtained. By annealing said granules or beads in a drier or the like at the annealing temperature for 30 minutes to 2 hours, sustained-release preparations can be obtained.

Under a microscopic observation, it can be seen that the granules before being annealed have a rough surface which is pierced deeply with many holes, however, the surface of the granules after being annealed are very smooth. It can be considered that this is because only the fat having a lower melting point located at the surface of the granule is melted and flows into the holes in the annealing process, thereby a certain amount of the active ingredient located in the outer parts of the granule comes out. Incidentally, the surface of the granule becomes very smooth even microscopically. That is to say, the granules of this invention each is structured, from the outside, by (a) a smooth layer where fine solids of the active ingredient and of the two different kinds of fats are very closely gathered and (b) a matrix core which is rather roughly structured by the active ingredient and the fats.

From the structure, it is presumed that the active ingredient is released from the preparations by the following mechanism:

When a preparation reaches the stomach, the gastric juice dissolves the exposed active ingredient, and the dissolved ingredient is released rapidly. Then, the juice permeates into the matrix core through the smooth layer and dissolves the ingredient gradually. The dissolved active ingredient is dispersed in the rough core and then released out gradually through the smooth layer. At this stage, the concentration of the active ingredient in the rough core is kept in a steady state, whereby, as a result, a zero-order releasing pattern is attained over a long period of time. It is to be noted here that the above presumption on the mechanism is not intended to limit the scope of this invention.

As regards active ingredients to be used in this invention, any active ingredient can be used as

long as it is soluble in water, and it is preferable if the active ingredient is such as can be absorbed through an extensive area of the digestive tract. The term "water-soluble active ingredient" as used in this invention includes not only pharmaceutical substances ordinarily soluble in water but also those which are sparingly water-soluble at or around the neutral point, but are soluble in acidic or alkaline aqueous medium (in the stomach or the intestines).

Representatives of such pharmaceutical substances are exemplified below, but these do not limit the scope this invention in any way:

Antihistamines such as chlorpheniramine maleate, d-chlorpheniramine maleate (hereinafter abbreviated as d-CPM), clemastine fumarate, carbinoxamine maleate, promethazine hydrochloride, and diphenhydramine salicylate (hydrochloride); analgesics and antipyretics such as aspirin, salicylamide, ethenzamide, acetaminophen, and diclofenac sodium; antitussives and expectorants such as dextromethorphan hydrobromide, dihydrocodeine phosphate, cloperastine hydrochloride, phenylpropanolamine hydrochloride (hereafter abbreviated as PPA), methylephedrine hydrochloride, potassium cresol sulfonate, potassium guaiacolate sulfonate, and belladonna total alkaloids; drugs for gastric ulcers such as pirenzepine hydrochloride, cetraxate, ranitidine, and famotidine; drugs for circulatory organs such as pindolol, propranolol hydrochloride, alprenolol hydrochloride, oxprenolol hydrochloride, diltiazem hydrochloride, and pinacidil; antitumor drugs such as cisplatin, 5-fluorouracil, and tegafur; and synthetic antibacterial agents such as cinoxacin and enoxacin.

Since the sustained-release preparations of this invention are not dependent on pH, they are expected to exhibit the same releasing properties in aged patients or patients with gastric subacidity or anacidity as in healthy adults.

This invention is explained in more detail by the following Examples or Experiments, which are not intended to limit the scope of this invention.

#### Examples (General Procedures)

##### - Granulation Process -

A fat of a higher melting point (hereafter mentioned as fat A) and a fat of a lower melting point (hereafter mentioned as fat B) are placed in a 1 L stainless mug and heated up to 90 - 120° C (melting temperature) with a mantle heater to give a melt. An active ingredient with a size through 80 mesh is suspended or melted in the melt, during the time of which the melt is kept at a temperature

of 100 -120 °C under stirring (500 r.p.m.) with a screw-type stirrer. The suspension or melt thus obtained is manufactured into beads of 300 -500  $\mu\text{m}\phi$  in diameter, using an atomizing type spray cooling apparatus equipped with a single fluid nozzle at a spraying temperature of 110 °C and a cooling temperature of 20 - 40 °C. 5

- Annealing Process -

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Thus obtained beads are treated in a drier at the annealing temperature for 30 minutes to 2 hours (treating time) and then cooled to room temperature to give a sustained-release preparation. 15

Examples 1 - 7

Sustained-release preparations shown in Table 1 were manufactured by the afore-mentioned General Procedures. 20

In these Examples or Reference Examples, the following substances were used:

As hydrogenated castor oil, Lovely Wax® 101 (melting point 79 -88 °C: Freund Sangyo); as hydrogenated beef oil, Triphate® -52 (melting point 49 - 54 °C: Nikko Chemical); as carnauba wax, Polishing Wax® 103 (melting point 80 - 86 °C: Freund Sangyo); as beeswax, Bleached Beeswax (melting point 60 - 67 °C: Miki Chemical); and as glycerol dipalmitate, a material of special reagent grade (melting point 50 -55 °C: Bansei Chemical). 25 30 35

Reference Examples 1 - 3

In substantially the same manner as in General Procedures reference compositions shown in Table 1 were manufactured. 40 45 50 55 5

Table 1

	THIS INVENTION				
	Example 1	Example 2	Example 3	Example 4	Example 5
Active Ingredient	PPA: 200g	PPA: 200g	PPA: 200g	PPA: 200g	PPA: 200g
Fat A	Hydrogenated castor oil: 240g	Hydrogenated cator oil: 320g	Carnauba wax: 250g	Stearic acid: 80g	Carnauba wax: 250g
Fat B	Hydrogenated beef oil: 60g	Hydrogenated beef oil: 80g	Bees wax: 62g	Glycerol dipal- mitate: 80g	Bees wax: 120g
Temp. for Melting	100°C	100°C	100°C	100°C	100°C
Spraying Temp.	110°C	110°C	110°C	110°C	110°C
Cooling Temp.	30°C	30°C	25°C	20°C	25°C
Annealing Temp.	65°C	65°C	70°C	45°C	70°C
Treating Time	2 Hours	2 Hours	1 Hour	0.5 Hours	1 Hour
Mean Particle Size	450 $\mu$ m $\phi$	450 $\mu$ m $\phi$	450 $\mu$ m $\phi$	450 $\mu$ m $\phi$	500 $\mu$ m $\phi$
Granules Obtained	440g	546g	473 g	607 g	512 g

Table 1 (Continued)

	THIS INVENTION		Control (PRIOR ART)		
	Example 6	Example 7	Reference 1	Reference 2	Reference 3
Active Ingredient	d-CPM: 100g	Vitamin B <sub>1</sub> mono-nitrate: 100g	PPA: 200g	PPA: 200g	PPA: 200g
Fat A	Hydrogenated castor oil: 320g	Carnauba wax: 210g	Hydrogenated castor oil: 400g	Hydrogenated castor oil: 400g	Hydrogenated castor oil: 240g
Fat B	Hydrogenated beef oil: 80g	Cetyl Alcohol: 140g	—	—	Hydrogenated beef oil: 60g
Temp. for Melting	100°C	100°C	100°C	100°C	100°C
Spraying Temp.	110°C	110°C	110°C	110°C	110°C
Cooling Temp.	30°C	30°C	30°C	30°C	30°C
Annealing Temp.	65°C	60°C	—	—	—
Treating Time	1 Hour	1 Hour	—	—	—
Mean Particle Size	450 $\mu$ m $\phi$	450 $\mu$ m $\phi$	450 $\mu$ m $\phi$	450 $\mu$ m $\phi$	450 $\mu$ m $\phi$
Granules Obtained	430g	400g	550g	550g	420g

## Example 8

## (Manufacturing of long-acting preparations)

To the 500g of the sustained-release beads prepared in Example 2 is powder-coated, by using a super mixer, a mixture of d-CPM (5g), hydrogenated castor oil (10g), and lactose (22g) each of which was passed through 80 mesh screen, during the time of which 65g of 2% aqueous solution of methylcellulose as a binder is sprayed to the same at a rate of 12g per minute. Thus obtained preparations are dried and dressed under aeration at 55°C for an hour to give twice-layered beads having a mean particle size of 500  $\mu\text{m}\phi$ . Thus obtained beads are distributed into capsules (no.4) by 451mg each to give the objective long-acting preparation. Each capsule preparation contains 70mg of PPA and 4 mg of d-CPM.

## Experiment 1

The preparations obtained in Examples 1 - 5 were subjected to dissolution test (paddle method), using the second fluid according to the Pharmacopoeia of Japan, 11th Edition. In each test, such an amount of beads as to contain 50 mg of PPA was used. Every preparation released rapidly 15 to 45% of the active ingredient in 10 minutes, and then the remainder did gradually in a practically zero-order release. The results are shown in Fig. 1.

## Experiment 2

Dissolution test (paddle method) in the first and the second fluids was carried out on the preparation obtained in Example 6, according to the Pharmacopoeia of Japan, 11th Edition. In each test, such an amount of beads as to contain 5 mg of d-CPM therein was used. In both tests, the preparation released rapidly 10% of the active ingredient within 10 minutes and then the remainder in a pattern close to zero-order. From the above, it was confirmed that the preparations of this invention are independent on pH conditions. The results are shown in Fig. 2.

## Experimental 3

Dissolution test (paddle method) in the second fluid was carried out on the preparations obtained

in Reference Examples 1 to 3, according to the Pharmacopoeia of Japan, 11th Edition. In each test, such an amount of beads as to contain 50mg of PPA therein was used. The results are shown in Fig. 3. These preparations released out almost all of the active ingredient in about 5 hours in a first-order release. Needless to say, they never have a sustained-release property.

## Claims

1. A sustained-release preparation essentially consisting of 1 part by weight of a water-soluble active ingredient and 1 to 10 parts by weight of two or more fats where the melting point is different in one from others.

2. The sustained-release preparation as claimed in Claim 1, wherein the fats are characterized by being a mixture of 1 part by weight of a fat having a higher melting point and 0.05 to 1 part by weight of a fat having a lower melting point.

3. A process for manufacturing sustained-release preparations, characterized in that 1 part by weight of a water-soluble active ingredient is suspended or melted in 1 to 10 parts by weight of a mixed melt consisting of two or more fats having different melting points, and while the temperature of the suspension or the melt is maintained at a level higher than the solidification point of the fat having a higher melting point, said suspension or melt is formulated into granules by means of spray-cooling, and then the granules obtained are annealed at a temperature which is lower than the melting point of the fat having a higher melting point but is higher than the melting point of the fat having a lower melting point.

4. The process as claimed in Claim 3, wherein the mixture of fats comprises 1 part by weight of a fat having a higher melting point and 0.05 to 1 part by weight of a fat having a lower melting point.



FIG 1

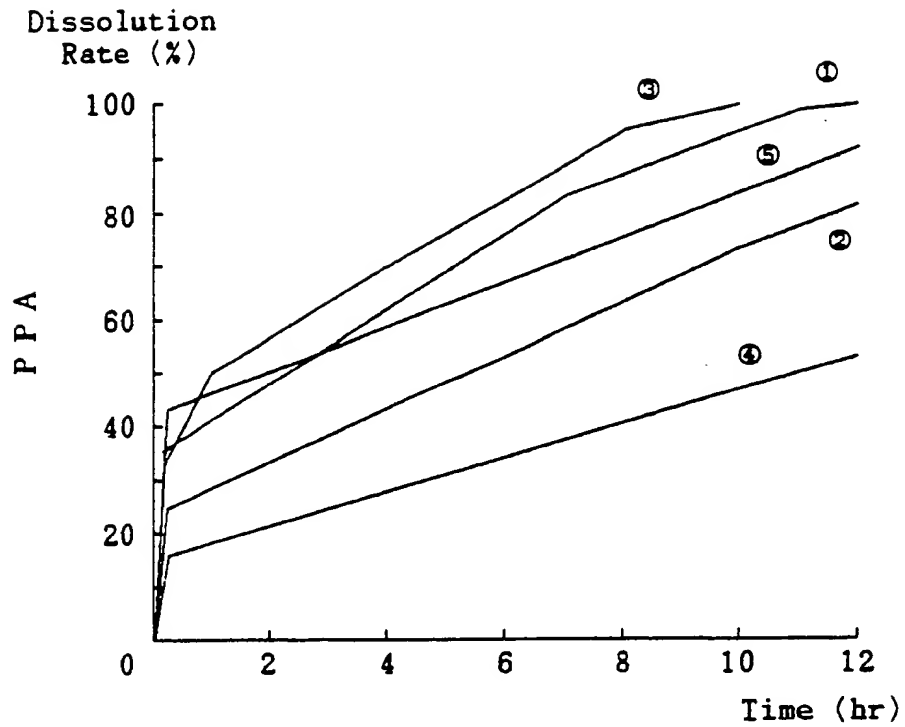


FIG 2

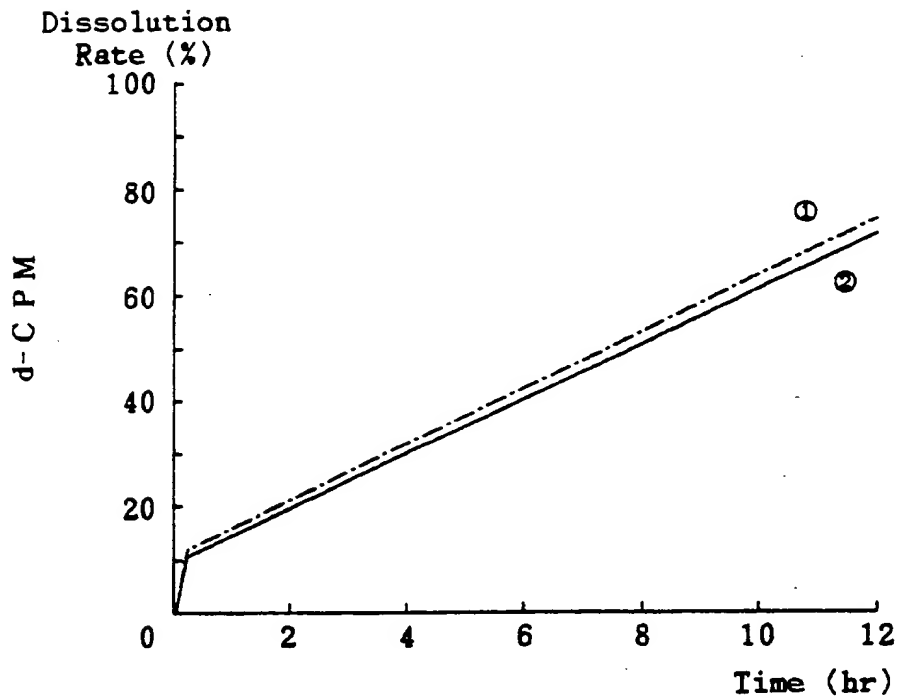
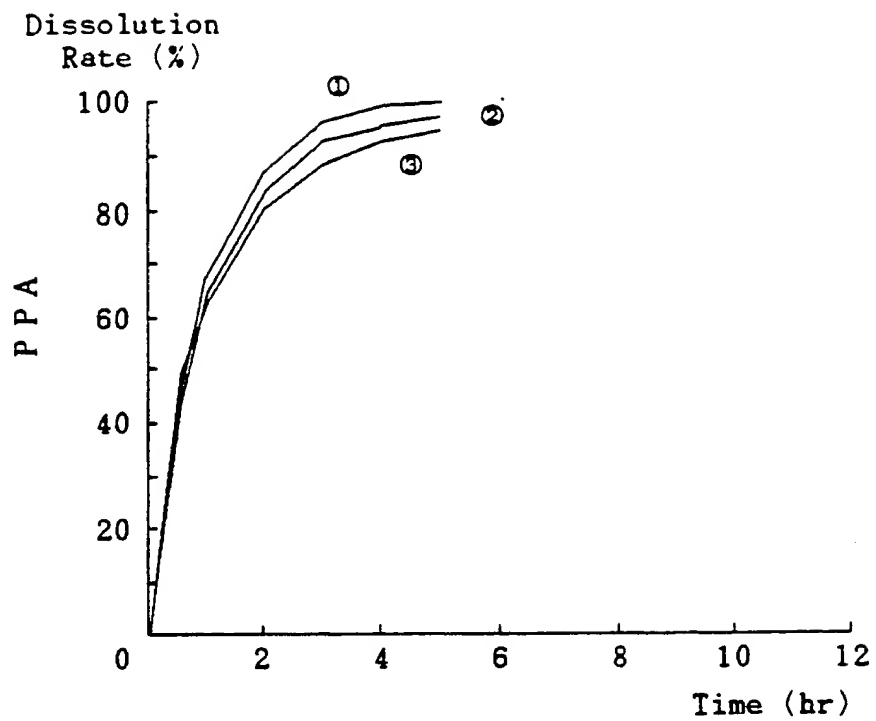


FIG 3



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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	EP-A-0 043 254 (GÖDECKE AG) * Page 4, line 23 - page 5, line 30; claims * ---	1-4	A 61 K 9/22
P,X	WO-A-8 902 742 (PHARMAGYN) * Claim * ---	1-4	
X	EP-A-0 254 978 (EISAI & CO.) * Pages 2,3; claim * ---	1-4	
X	CHEMICAL ABSTRACTS, vol. 84, no. 12, 22nd March 1976, page 385, abstract no. 79641a, Columbus, Ohio, US; K. KUMAR et al.: "Sustained release tablet formulation of diethylcarbamazine citrate (hetrazan)", & INDIAN J. PHARM. 1975, 37(3), 57-9 * Abstract * ---	1-4	
X	CHEMICAL ABSTRACTS, vol. 92, no. 6, 11th February 1980, page 331, abstract no. 47182a, Columbus, Ohio, US; M.S. SOCIAS et al.: "Galenic study of oral and sustained action pharmaceutical forms based on wax matrixes", & CIENC. IND. FARM. 1978, 10(10), 275-86 * Abstract * ---	1-4	TECHNICAL FIELDS SEARCHED (Int. Cl.5)  A 61 K
X	CHEMICAL ABSTRACTS, vol. 95, no. 1, 13th July 1981, page 359, abstract no. 12671u, Columbus, Ohio, US; M. AHMED et al.: "Formulation and evaluation of sustained release paracetamol tablets", & J. CLIN. HOSP. PHARM. 1981, 6(1), 27-38 * Abstract * -----	1-4	
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 22-02-1990	Examiner BERTE M.J.
<b>CATEGORY OF CITED DOCUMENTS</b> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document  T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ..... & : member of the same patent family, corresponding document			

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